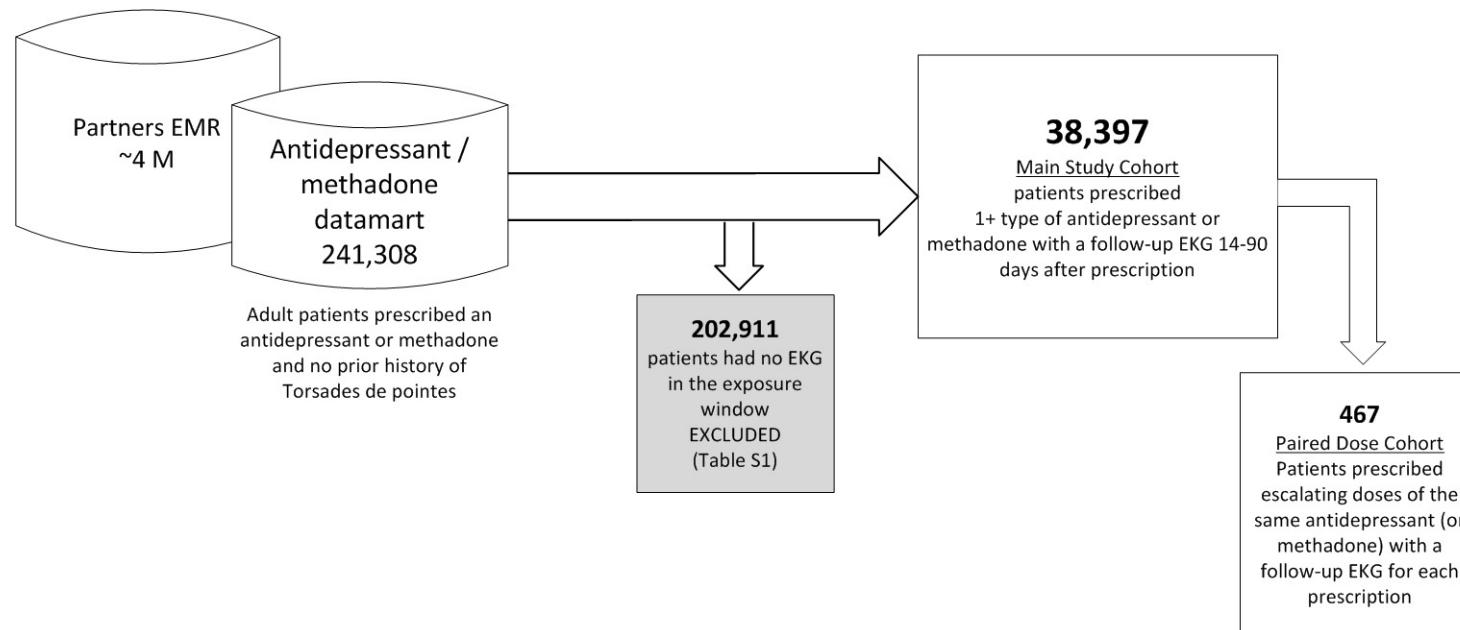
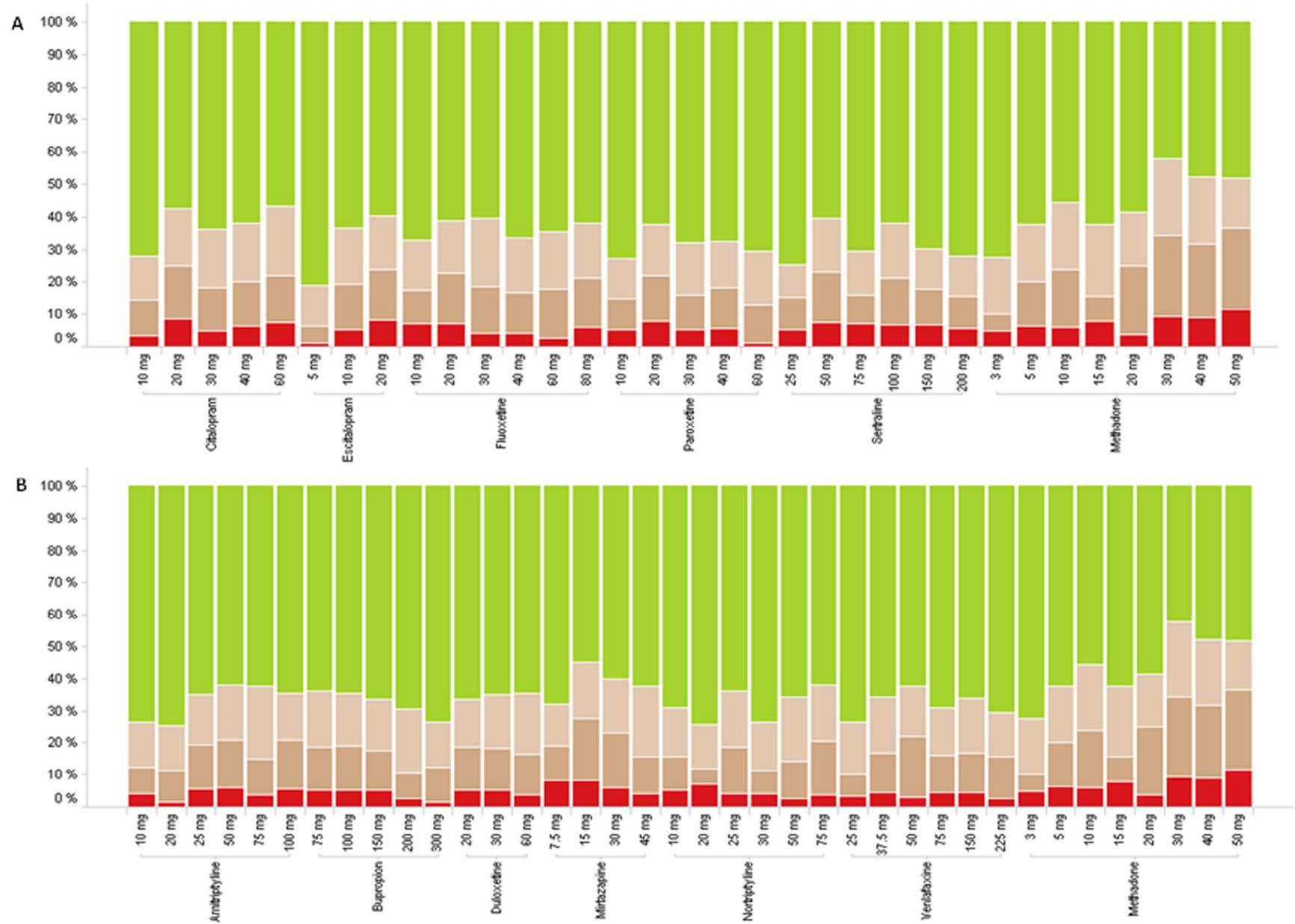


## Supplementary figures and tables

**Figure A:** Study schematic



**Figure B:** Percent of patients with a normal (green), borderline (beige), abnormal (brown), or high (red) electrocardiogram 14-90 days after prescription of (A) an SSRI or methadone (positive control) by dose or (B) other antidepressants or methadone, by dose



**Table A:** Demographic and clinical feature comparisons between study cohort and patients receiving an antidepressant or methadone but no EKG in the drug exposure window\*

	<b>Antidepressant/ methadone users with EKG (14-90 days post-dose)</b>	<b>Antidepressant/ methadone users with no EKG in exposure window</b>	<b>p-value</b>
<b>N</b>	38,397	202,911	
<b>Demographics</b>			
Age, mean years (SD)			
Female gender	58.3 (16.2)	49.4 (17.2)	< 0.001 †
Race/ethnicity <sup>§§</sup>	23,020 (60.0)	134,564 (66.3)	< 0.001 ††
White	30,637 (80.0)	163,874 (80.8)	< 0.001 ††
African American	2,759 (7.2)	9,262 (4.6)	
Hispanic	2,987 (7.8)	12,911 (6.4)	
Asian	451 (1.2)	2,772 (1.4)	
Other	1,528 (4.0)	14,172 (7.0)	
Insurance			< 0.001 ††
Public	20,052 (52.2)	69,559 (34.3)	
Private	15,851 (41.3)	115,615 (57.0)	
Other / Unknown	2,494 (6.5)	17,817 (8.8)	
Year of EKG, median (IQR)	2007 (2004-2009)	2007 (2004-2009)	< 0.001 †††
<b>Comorbidities (lifetime history)</b>			
Major depression	10,930 (28.5)	34,772 (17.1)	< 0.001 ††
Myocardial infarction	10,391 (27.1)	15,535 (7.7)	< 0.001 ††
Ventricular arrhythmia	7,968 (20.8)	53,085 (26.2)	< 0.001 ††
Hypertension	28,145 (73.3)	81,384 (40.1)	< 0.001 ††
Hyperlipidemia	23,384 (60.9)	72,499 (35.7)	< 0.001 ††
Age-adjusted Charlson comorbidity index	6 (3-10)	2 (0-5)	< 0.001 †††
<b>Pharmacotherapy</b>			
SSRI			
Citalopram	9,777 (25.5)	48,690 (24.3)	
Escitalopram	2,364 (6.2)	15,821 (7.8)	
Fluoxetine	5,721 (14.9)	35,230 (17.4)	
Paroxetine	4,205 (11.0)	21,793 (10.7)	
Sertraline	6,293 (16.4)	36,034 (17.8)	
Other antidepressants			
Duloxetine	1,912 (5.0)	10,402 (5.1)	
Venlafaxine	2,480 (6.5)	15,853 (7.8)	
Bupropion	5,064 (13.2)	35,259 (17.4)	
Mirtazapine	3,487 (9.1)	11,337 (5.6)	
Amitriptyline	4,228 (11.0)	25,206 (12.4)	
Nortriptyline	1,978 (5.2)	12,632 (6.2)	
Opiate antagonist			
Methadone (known QTc-prolonging agent)	2,255 (5.9)	7,830 (3.9)	

\*All values indicate patient count (% of cohort) unless otherwise specified.

†comparison using Students' t-test; ††comparison using  $\chi^2$ ; ††† Comparison using Kruskal-Wallis non-parametric test

§§ Race and ethnicity are collected using a single field in the electronic health record, so subjects who identify as Hispanic are not further characterized.

**Table B:** Overall effect of medication dose on continuous QTc measured **14-30** days after medication dose

Antidepressant	Unadjusted model		Adjusted model†	
	Beta (SE)		Beta (SE)	
SSRI				
Citalopram	0.04 (0.04)		0.10 (0.04)	**
Escitalopram	0.60 (0.17)	***	0.62 (0.17)	***
Fluoxetine	-0.03 (0.03)		0.04 (0.03)	
Paroxetine	-0.05 (0.07)		0.04 (0.07)	
Sertraline	-0.02 (0.01)		0.01 (0.01)	
TCA/Other				
Amitriptyline	0.12 (0.03)	***	0.12 (0.03)	***
Bupropion	-0.03 (0.01)	***	-0.02 (0.01)	*
Duloxetine	0.00 (0.05)		0.02 (0.05)	
Mirtazapine	-0.12 (0.08)		-0.03 (0.08)	
Nortriptyline	0.01 (0.04)		0.06 (0.04)	
Venlafaxine	0.01 (0.01)		0.01 (0.01)	
<b>Positive control</b>				
Methadone	0.30 (0.06)	***	0.31 (0.06)	***

Statistical significance at \*\*\*  $\alpha = 0.001$ ; \*\*  $\alpha = 0.01$ ; \*  $\alpha = 0.05$

† Model is adjusted for age, gender, race, type of insurance, year of EKG, history of major depression, history of myocardial infarction, history of ventricular arrhythmia, history of hypertension, and history of hyperlipidemia and log-transformed age-adjusted Charlson comorbidity score.

**Table C:** Overall effect of medication dose on continuous QTc measured 14-90 days after medication dose. Prescriptions with a concomitant prescription of a typical or atypical antipsychotic or other known QT prolonging agent are excluded.

<b>Antidepressant</b>	<b>Unadjusted model</b>		<b>Adjusted model†</b>	
	<b>Beta (SE)</b>		<b>Beta (SE)</b>	
<b>SSRI</b>				
Citalopram	0.01 (0.04)		0.08 (0.04)	*
Escitalopram	0.49 (0.17)	**	0.54 (0.17)	***
Fluoxetine	0.02 (0.04)		0.09 (0.04)	*
Paroxetine	0.00 (0.08)		0.08 (0.08)	
Sertraline	-0.03 (0.01)	*	0.01 (0.01)	
<b>TCA/Other</b>				
Amitriptyline	0.09 (0.03)	***	0.10 (0.03)	***
Bupropion	-0.02 (0.01)		0.00 (0.01)	
Duloxetine	0.03 (0.05)		0.04 (0.05)	
Mirtazapine	-0.26 (0.11)	*	-0.13 (0.11)	
Nortriptyline	-0.04 (0.05)		0.02 (0.04)	
Venlafaxine	0.01 (0.01)		0.01 (0.01)	

Statistical significance at \*\*\*  $\alpha = 0.001$ ; \*\*  $\alpha = 0.01$ ; \*  $\alpha = 0.05$

† Model is adjusted for age, gender, race, type of insurance, year of EKG, history of major depression, history of myocardial infarction, history of ventricular arrhythmia, history of hypertension, and history of hyperlipidemia and log-transformed age-adjusted Charlson comorbidity score.

**Table D:** Overall effect of medication dose on continuous QTc measured 14-90 days after medication dose where a prescription re-fill occurs with 30 days of the end of supply

<b>Antidepressant</b>	<b>Unadjusted model</b>	<b>Adjusted model†</b>		
	<b>Beta (SE)</b>	<b>Beta (SE)</b>		
<b>SSRI</b>				
Citalopram	0.04 (0.04)	0.10 (0.04)	**	
Escitalopram	0.60 (0.17)	***	0.62 (0.17)	***
Fluoxetine	-0.03 (0.03)	0.04 (0.03)	*	
Paroxetine	-0.05 (0.07)	0.04 (0.07)		
Sertraline	-0.02 (0.01)	0.01 (0.01)		
<b>TCA/Other</b>				
Amitriptyline	0.12 (0.03)	***	0.12 (0.03)	***
Bupropion	-0.03 (0.01)	***	-0.02 (0.01)	*
Duloxetine	-0.00 (0.05)	0.02 (0.05)		
Mirtazapine	-0.12 (0.08)	-0.03 (0.08)		
Nortriptyline	0.01 (0.04)	0.06 (0.04)		
Venlafaxine	0.01 (0.01)	0.01 (0.01)		
<b>Positive control</b>				
Methadone	0.30 (0.06)	***	0.31 (0.06)	***

Statistical significance at \*\*\*  $\alpha = 0.001$ ; \*\*  $\alpha = 0.01$ ; \*  $\alpha = 0.05$

† Model is adjusted for age, gender, race, type of insurance, year of EKG, history of major depression, history of myocardial infarction, history of ventricular arrhythmia, history of hypertension, and history of hyperlipidemia and log-transformed age-adjusted Charlson comorbidity score.